CLAIMS

What is claimed is:

1. A method for determining the free energy of binding of a potential ligand to a receptor, comprising the steps of:

obtaining, for each of two or more actual receptor ligands, at least one of a structure and a free energy of binding to said receptor, such that each of said two or more actual receptor ligands has a known structure and a known free energy of binding to said receptor;

orienting said structures of said two or more actual receptor ligands for maximum geometric coincidence with each other;

determining an electrostatic potential at each of more than one point on a van der Waals surface of each of said actual receptor ligands;

thereafter, mapping each of said electrostatic potentials of each of said actual receptor ligands onto a geometric surface of one of said two or more actual receptor ligands, each of said two or more actual receptor ligands being thereby described by an identical surface geometry but a different electrostatic potential surface, and each of said electrostatic potentials being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials, said positional information, and said known free energy of binding of one of said two or more actual receptor ligands into a neural network;

thereafter, training said neural network until said neural network predicts said free energy of binding of said one of said two or more actual receptor ligands;

repeating said steps of inputting and training for each of the remaining said two or more actual receptor ligands to produce a trained network;

thereafter, determining a potential ligand electrostatic potential at each of more than one point on a van der Waals surface of said potential ligand, said potential ligand having a known structure and an unknown free energy of binding to said receptor;

orienting said structure of said potential ligand for maximum geometric coincidence with said structures of said two or more actual receptor ligands;

thereafter, mapping each of said electrostatic potentials of said potential ligand onto a geometric surface of one of said two or more actual receptor ligands, said potential ligand having a surface geometry identical to that of said two or more actual receptor ligands, but a different electrostatic potential surface, and each of said electrostatic potentials of said potential ligand being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials and said positional information of said electrostatic potentials of said potential ligand into said trained network; and

using said trained network to calculate a free energy of binding of said potential ligand to said receptor.

2. A method for determining the free energy of binding of a potential ligand to a receptor, comprising the steps of:

obtaining a structure for said potential ligand;

orienting structures of two or more actual receptor ligands for said receptor for maximum geometric coincidence with each other;

each of said two or more actual receptor ligands having a known structure and a known free energy of binding to said receptor;

determining an electrostatic potential at each of more than one point on a van der Waals surface of each of said actual receptor ligands;

thereafter, mapping each of said electrostatic potentials of each of said actual receptor ligands onto a geometric surface of one of said two or more actual receptor ligands, each of said two or more actual receptor ligands being thereby described by an identical surface geometry but a different electrostatic potential surface, and each of said electrostatic potentials being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials, said positional information, and said known free energy of binding of one of said two or more actual receptor ligands into a neural network;

thereafter, training said neural network until said neural network predicts said free energy of binding of said one of said two or more actual receptor ligands;

repeating said steps of inputting and training for each of the remaining said two or more actual receptor ligands to produce a trained network;

thereafter, determining an potential ligand electrostatic potential at each of more than one point on a van der Waals surface of said potential ligand, said potential ligand having an unknown free energy of binding to said receptor;

orienting said structure of said potential ligand for maximum geometric coincidence with said structures of said two or more actual receptor ligands;

thereafter, mapping each of said electrostatic potentials of said potential ligand onto a geometric surface of one of said two or more actual receptor ligands, said potential ligand having a surface geometry identical to that of said two or more actual receptor ligands, but a different electrostatic potential surface, and each of said electrostatic potentials of said potential ligand being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials and said positional information of said electrostatic potentials of said potential ligand into said trained network; and

using said trained network to calculate a free energy of binding of said potential ligand to said receptor.

3. A computer readable medium, comprising:

computer-readable information;

said information capable of interacting with a computer to produce an output;

said output being a calculated free energy of binding of a potential ligand to a receptor;

said output being calculated by:

orienting structures of said two or more actual receptor ligands for maximum geometric coincidence with each other;

each of said two or more actual receptor ligands having a known structure and a known free energy of binding to said receptor;

determining an electrostatic potential at each of more than one point on a van der Waals surface of each of said actual receptor ligands;

thereafter, mapping each of said electrostatic potentials of each of said actual receptor ligands onto a geometric surface of one of said two or more actual receptor ligands, each of said two or more actual receptor ligands being thereby described by an identical surface geometry but a different electrostatic potential surface, and each of said electrostatic potentials being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials, said positional information, and said known free energy of binding of one of said two or more actual receptor ligands into a neural network;

thereafter, training said neural network until said neural network predicts said free energy of binding of said one of said two or more actual receptor ligands;

repeating said steps of inputting and training for each of the remaining said two or more actual receptor ligands to produce a trained network;

thereafter, determining an potential ligand electrostatic potential at each of more than one point on a van der Waals surface of said potential ligand, said potential ligand having a known structure and an unknown free energy of binding to said receptor;

orienting said structure of said potential ligand for maximum geometric coincidence with said structures of said two or more actual receptor ligands;

thereafter, mapping each of said electrostatic potentials of said potential ligand onto a geometric surface of one of said two or more actual receptor ligands, said potential ligand having a surface geometry identical to that of said two or more actual receptor ligands, but a different electrostatic potential surface, and each of

said electrostatic potentials of said potential ligand being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials and said positional information of said electrostatic potentials of said potential ligand into said trained network; and

using said trained network to calculate a free energy of binding of said potential ligand to said receptor.

4. A method for determining a free energy of binding of a potential transition-state inhibitor to an enzyme, comprising the steps of:

obtaining, for each of two or more enzyme substrates or inhibitors, at least one of a structure and a free energy of binding to said enzyme, such that each of said two or more enzyme substrates or inhibitors has a known structure and a known free energy of binding to said enzyme;

orienting said structures of said two or more enzyme substrates or inhibitors for maximum geometric coincidence with each other;

determining an electrostatic potential at each of more than one point on a van der Waals surface of each of said enzyme substrates or inhibitors;

thereafter, mapping each of said electrostatic potentials of each of said enzyme substrates or inhibitors onto a geometric surface of a transition state inhibitor, each of said enzyme substrates or inhibitors being thereby described by an identical surface geometry but a different electrostatic potential surface, and each of said electrostatic potentials being described by positional information relating said electrostatic potentials to said geometric surface of said transition state inhibitor;

thereafter, inputting said electrostatic potentials, said positional information, and said known free energy of binding of one of said two or more enzyme substrates or inhibitors into a neural network;

thereafter, training said neural network until said neural network predicts said free energy of binding of said one of said two or more enzyme substrates or inhibitors;

repeating said steps of inputting and training for each of the remaining said two or more enzyme substrates or inhibitors to produce a trained network;

thereafter, determining an potential transition electrostatic potential at each of more than one point on a van der Waals surface of said potential transition-state inhibitor, said potential transition-state inhibitor having a known structure and an unknown free energy of binding to said enzyme;

orienting said structure of said potential transition-state inhibitor for maximum geometric coincidence with said structures of said two or more enzyme substrates or inhibitors;

thereafter, mapping each of said electrostatic potentials of said potential transition-state inhibitor onto a geometric surface of one of said two or more two or more enzyme substrates or inhibitors, such that said potential transition-state inhibitor has a surface geometry identical to that of said two or more actual receptor transition-state inhibitors, but a different electrostatic potential surface, and each of said electrostatic potentials of said potential transition-state inhibitor is described by positional information relating said electrostatic potentials to said geometric surface of said two or more enzyme substrates or inhibitors;

thereafter, inputting said electrostatic potentials and said positional information of said electrostatic potentials of said potential transition-state inhibitor into said trained network; and

using said trained network to calculate a free energy of binding of said potential transition-state inhibitor to said enzyme.

5. A method for determining the free energy of binding of a potential transition-state inhibitor to a enzyme, comprising the steps of:

obtaining a structure for said potential transition-state inhibitor;

orienting structures of two or more enzyme substrates or inhibitors for said enzyme for maximum geometric coincidence with each other;

each of said two or more enzyme substrates or inhibitors having a known structure and a known free energy of binding to said enzyme;

determining an electrostatic potential at each of more than one point on a van der Waals surface of each of said enzyme substrates or inhibitors;

thereafter, mapping each of said electrostatic potentials of each of said enzyme substrates or inhibitors onto a geometric surface of one of said two or more enzyme substrates or inhibitors, each of said two or more enzyme substrates or inhibitors being thereby described by an identical surface geometry but a different electrostatic potential surface, and each of said electrostatic potentials being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials, said positional information, and said known free energy of binding of one of said two or more enzyme substrates or inhibitors into a neural network;

thereafter, training said neural network until said neural network predicts said free energy of binding of said one of said two or more enzyme substrates or inhibitors;

repeating said steps of inputting and training for each of the remaining said two or more enzyme substrates or inhibitors to produce a trained network;

thereafter, determining an potential transition-state inhibitor electrostatic potential at each of more than one point on a van der Waals surface of said potential transition-state inhibitor, said potential transition-state inhibitor having an unknown free energy of binding to said enzyme;

orienting said structure of said potential transition-state inhibitor for maximum geometric coincidence with said structures of said two or more enzyme substrates or inhibitors;

thereafter, mapping each of said electrostatic potentials of said potential transition-state inhibitor onto a geometric surface of one of said two or more enzyme substrates or inhibitors, said potential transition-state inhibitor having a surface geometry identical to that of said two or more enzyme substrates or inhibitors, but a different electrostatic potential surface, and each of said electrostatic potentials of said potential transition-state inhibitor being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials and said positional information of said electrostatic potentials of said potential transition-state inhibitor into said trained network; and

using said trained network to calculate a free energy of binding of said potential transition-state inhibitor to said enzyme.

6. A computer readable medium, comprising:

computer-readable information;

said information capable of interacting with a computer to produce an output;

said output being a calculated free energy of binding of a potential transition-state inhibitor to a enzyme;

said output being calculated by:

orienting structures of said two or more actual receptor ligands for maximum geometric coincidence with each other;

each of said two or more actual ligands having a known structure and a known free energy of binding to said enzyme;

determining an electrostatic potential at each of more than one point on a van der Waals surface of each of said enzyme substrates or inhibitors;

thereafter, mapping each of said electrostatic potentials of each of said enzyme substrates or inhibitors onto a geometric surface of one of said two or more enzyme substrates or inhibitors, each of said two or more enzyme substrates or inhibitors being thereby described by an identical surface geometry but a different electrostatic potential surface, and each of said electrostatic potentials being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials, said positional information, and said known free energy of binding of one of said two or more enzyme substrates or inhibitors into a neural network;

thereafter, training said neural network until said neural network predicts said free energy of binding of said one of said two or more enzyme substrates or inhibitors;

repeating said steps of inputting and training for each of the remaining said two or more enzyme substrates or inhibitors to produce a trained network;

thereafter, determining an potential transition-state inhibitor electrostatic potential at each of more than one point on a van der Waals surface of said potential receptor ligand, said potential receptor ligand having a known structure and an unknown free energy of binding to said enzyme;

orienting said structure of said potential transition-state inhibitor for maximum geometric coincidence with said structures of said two or more enzyme substrates or inhibitors;

thereafter, mapping each of said electrostatic potentials of said potential transition-state inhibitor onto a geometric surface of one of said two or more enzyme substrates or inhibitors, said potential transition-state inhibitor having a surface geometry identical to that of said two or more enzyme substrates or inhibitors, but a different electrostatic potential surface, and each of said electrostatic potentials of said potential transition-state inhibitor being described by positional information relating said electrostatic potentials to said geometric surface;

thereafter, inputting said electrostatic potentials and said positional information of said electrostatic potentials of said potential transition-state inhibitor into said trained network; and

using said trained network to calculate a free energy of binding of said potential transition-state inhibitor to said enzyme.

7. A method for determining the free energy of binding of a potential ligand to a receptor according to claim 1, wherein said neural network is a feed forward network with back propagation of error that learns with momentum.

8. A method for determining the free energy of binding of a potential ligand to a receptor according to claim 2, wherein said neural network is a feed forward network with back propagation of error that learns with momentum.

9. A method for determining the free energy of binding of a potential transition-state inhibitor to a enzyme according to claim 4, wherein said neural network is a feed forward network with back propagation of error that learns with momentum.

10. A method for determining the free energy of binding of a potential transition-state inhibitor to a enzyme according to claim 5, wherein said neural network is a feed forward network with back propagation of error that learns with momentum.

11. A computer readable medium according to claim 3, wherein said neural network is a feed forward network with back propagation of error that learns with momentum.

12. A computer readable medium according to claim 6, wherein said neural network is a feed forward network with back propagation of error that learns with momentum.

13. A method for determining the free energy of binding of a potential ligand to a receptor according to claim 7, wherein said neural network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

14. A method for determining the free energy of binding of a potential ligand to a receptor according to claim 8, wherein said neural network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

15. A method for determining the free energy of binding of a potential transition-state inhibitor to a enzyme according to claim 9, wherein said neural network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

16. A method for determining the free energy of binding of a potential transition-state inhibitor to a enzyme according to claim 10, wherein said neural network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

17. A computer readable medium according to claim 11, wherein said neural network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.

18. A computer readable medium according to claim 12, wherein said neural network uses a learning rate between 0.1 and 0.5 and a momentum term between 0.8 and 0.9.